

REMARKS

Rejection of the claims under 35 USC § 112:

Claims 1, 4-6, 10, 13, and 14 has been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Action states that the specification does not disclose a reversibly modified RNA or define the term for a reversibly modified RNA. Applicants respectfully disagree. The specification, on page 2 lines 16-18, "...post-synthetically modified RNA oligonucleotides wherein the modifications are labile under mammalian physiological conditions. The modifications may be labile either through hydrolysis or enzymatic cleavage". It is the Applicants' opinion that the process of modifying or reversibly modifying an RNA is readily recognized by those skilled in the art as producing a modified or reversibly modified RNA. The process for modifying and reversibly modifying an RNA can be found in the specification on page 5 line 14 to page 9 line 8. Support can also be found in the specification on page 11 line 30 to page 12 line 2.

Claims 1, 4-6, 10, 13, and 14 has been rejected under 35 U.S.C. 112, second paragraph, as being indefinite, because the claim does not state "what" is associated through hydrophobic interactions. Applicants have amended to claims to obviate the rejection.

Rejection of the claims under 35 USC § 102:

Claims 1, 4-6, 10, 13, and 14 have been rejected under 35 U.S.C. 102(e) as being unpatentable over Fosnaugh et al. (U.S. 2003/0143732) as evidenced by Thierry et al. (US 6,110,490). Applicants respectfully disagree.

The courts found, In re Deuel, 51 F.3d 1552, 1558 (Fed. Cir. 1995), in cases involving new chemical compounds, that it remains necessary to identify some reason that would have led a one skilled in the art to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound. More recently, in Takeda v. Alphapharm, 492 F.3d 1350 (Fed.Cir. 2007) the courts found that there is no *prima facie* obviousness found when the prior art teaches many compounds, only one of which, when modified, may lead to patentee's compound. Fosnaugh et al. teach siRNA-lipid conjugates [paragraph 0109] as well as a large number of other siRNA conjugates - essentially, without limitation, any modification so long as

the siRNA still regulates ADORA1 gene expression. Fosnaugh et al. further teach that siRNA molecules of their invention can be complexed with cationic lipids [0124] or “otherwise delivered to target cells or tissues.” Fosnaugh et al. teach that any known delivery method is suitable with their invention. Fosnaugh et al. do not teach or provide any motivation or desire for the specific combination of a lipid-siRNA with a cationic lipid. Fosnaugh et al. also do not specifically teach an RNA conjugated to a lipid via labile bond cleavable under mammalian physiological conditions.

The action states that Thierry et al. teach that liposomal complexes comprising oligonucleotides are formed by hydrophobic interactions. Applicants note that Thierry et al. do not in fact teach that liposomes complexes are formed by hydrophobic interactions. Nevertheless, it is well known in the art that liposomes themselves are in fact formed by hydrophobic interactions between the tail groups of the lipids. However, it is also well known in the art that the interactions between nucleic acids (oligonucleotides) and liposome lipids occur through electrostatic interactions between the negatively charged nucleic acid and the positively charged head groups of the liposome lipids; hence the specific selection of cationic lipids by Thierry et al. (see supporting references, Barichello et al. *Methods in Molecular Biology*, Chapter 2, 2010, Vol. 605, p. 461-472, and Pedroso de Lima et al. *Current Medicinal Chemistry* 2003, Vol. 10, p. 1221-1231.) Thierry et al. do not teach association of a nucleic acid with a liposome wherein the association is enhanced by a hydrophobic interaction between the liposome and a hydrophobic group attached to the nucleic acid.

Claims 1, 4-6, 10, 13, and 14 have been rejected under 35 U.S.C. 102(e) as being unpatentable over Lewis et al. (U.S. 2003/0143204) as evidenced by Thierry et al. (US 6,110,490). The Action states that the instant claims are interpreted to comprise an siRNA, a hydrophobic group, and a transfection reagent such as a cationic liposome. Applicants have amended the claims to clarify that association of the RNA with the transfection reagent is enhanced through hydrophobic interaction between the modified RNA and the transfection reagent.

The Action states. “Applicant argues that Lewis et al. do not teach the polymers can have labile bonds...” This statement is incorrect. Applicants previously argued, “Lewis et al. teach that

polymers *can* have labile bonds, *but* do not teach that a functional group can be attached to an RNA via a labile bond.” Applicants further maintain that while Lewis et al. (US 20030143201) teach that a functional group can be attached to an siRNA, Lewis et al. do not teach that the functional group can be a hydrophobic group.

Support for the amendments to the claims can be found in the specification on page 3 lines 24-32, page 4 lines 1-16, page 5 lines 15-17, and page 9 lines 10-15.

Rejection of the claims under 35 USC § 103:

Claims 1, 4-6, 10, 13, and 14 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Fosnaugh et al. (U.S. 2003/0143732) or Lewis et al. (US 20030143201), taken with Manoharan, M. (Biochimica et Biophysica Acta 1489, 1999: 117-130) and Goldsborough (WO 01/94626). It is the Applicants’ opinion that the amendments and arguments made above in response to the 102 rejections are sufficient to overcome the 103 rejections.

The Examiner’s rejections are now believed to be overcome by this response to the Office Action. In view of Applicants’ amendment and arguments, it is submitted that claims 1, 4-6, 10, 13, and 14 should be allowable.

Respectfully submitted,

/Kirk Ekena/
Kirk Ekena, Reg. No. 56,672
Roche Madison Inc.
465 Science Dr., Suite C
Madison, WI 53711
608-316-3896

I hereby certify that this correspondence is being
transmitted to the USPTO on this date: 27 Jan. 2010.

/Kirk Ekena/
Kirk Ekena